Immune Complexes of Hepatitis B Surface Antigen in the Pathogenesis of Periarteritis Nodosa

A Study of Seven Necropsy Cases

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In 7 unselected necropsy cases of clinically diagnosed periarteritis nodosa, the detection of hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) in the cytoplasm and nuclei of hepatocytes indicated an ongoing infection with hepatitis B virus (HBV). In all these cases histologic changes found in the liver varied from "minimal" to chronic aggressive hepatitis. In all the cases, deposits of HBsAg, immunoglobulins, β_{1C}-globulin and C1q were detected in vascular lesions. That these deposits could represent HBsAg–anti-HBs immune complexes was supported by demonstrating their strong binding of guinea pig complement and by the successful elution of all HBsAg and part of the immunoglobulin from these deposits by treatment with buffers known to dissociate antigen–antibody bonds but not with phosphate-buffered saline, pH 7.6 (PBS). Glomerulonephritis associated with these immune complexes was found in 6 cases. The presence of larger masses of HBsAg immune complexes, chiefly in recent insudative and fibrinoid vascular lesions, their lesser amounts in lesions undergoing involution, and their absence from healed lesions strongly suggest that these complexes play a primary role in the pathogenesis of acute vascular damage in periarteritis nodosa. (Am J Pathol 90:619–632, 1978)

RECENT REPORTS on the high incidence of HBsAg and circulating HBsAG–anti-HBs immune complexes in the serums [1-3] and on the occurrence of HBsAg, immunoglobulins, and complement in the vascular lesions of patients with periarteritis nodosa [4,5] support the hypothesis that the lesion complex of periarteritis nodosa can result from antigen–antibody interaction.[4,6] The present study was undertaken to further assess the role of HBsAg immune complexes in the pathogenesis of vascular lesions in this disease. Direct immunofluorescent staining, double-staining with paired reagents labeled with contrasting fluorochromes, heterologous complement fixation, and elution procedures were used to identify the HBsAg immune complexes in the examined tissue material.

Materials and Methods

Tissue and Serums

The material for this study consisted of necropsy specimens from 7 unselected cases of clinically diagnosed periarteritis nodosa. The specimens were from 1 female and 6 male patients aged 27 to 59 years.

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In each case, within 24 hours after death, five specimens were taken from the kidney and liver; two specimens each from the myocardium, pancreas, spleen, lymph nodes, and skeletal muscle; and one each from the brain and skin. Tissue blocks were fixed in the neutral 4% formalin, routinely processed, and embedded in paraffin. Serial paraffin sections were stained with hematoxylin and eosin, orcein by the Shikata method,[7] Masson-trichrome, orcein and the van Gieson method and were impregnated with silver by the Gomori method. Duplicate blocks were rapidly frozen at −80 C and sectioned in a cryostat at −25 C for immunohistochemical studies.

In 5 patients, the serum samples were assayed for HBsAg by immunoelectroosmophoresis (IEOP).[8] Routine laboratory studies of these serums were performed in the clinical laboratories.

Immunohistochemical Procedures

Direct immunofluorescence method was used for the tissue localization of HBsAg, IgG, IgM, IgA, β_{1C}-globulin, C1q component of complement, and fibrin. The globulin fractions of animal antiserums to these antigens were labeled with fluorescein isothiocyanate (FITC) or lissamine rhodamine (LRB). Methods of procedure, characteristics, and specificity control of the immunofluorescent reagents were described elsewhere.[9] Anti-C1q reagent was prepared according to the methods of Agnello et al.[10] In all instances, several consecutive frozen sections were stained with paired reagents labeled in contrasting colors (FITC and LRB).

The indirect procedure of heterologous complement fixation on tissue sections of Burkholder [11] was employed. Frozen tissue sections were incubated with fresh guinea pig serum diluted 1 : 15 with PBS and subsequently stained with FITC-labeled anti-guinea pig β_{1C}-globulin reagent. Control procedures consisted in directly staining the serial sections with anti-guinea pig β_{1C}-globulin reagent and using heat-inactivated guinea pig serum as an intermediate layer.

The results of staining were evaluated in a Leitz Ortholux microscope. Microphotographs were taken on Scopix G (Agfa–Gevaert) black and white 35-mm film.

Elution Procedures

The stability and the characteristics of antigen–antibody binding in tissue sections were studied by washing the unfixed cryostat sections with PBS and solutions known to dissociate immune complexes: 0.2 M HCl–glycine, pH 2.2; 2.5 M KSCN, pH 5.7; 3 M NaSCN, pH 7.4; and saturated $MgCl_2$ solution. The elution procedure consisted of two consecutive stages. First, the sections were washed in PBS for 1 hour at room temperature. Next, the same sections were eluted with the solutions dissociating immune complexes for 3 hours. The control of the effectivity of the elution consisted of washing the serial frozen sections with PBS for 4 hours. All sections were then fixed in acetone or anesthetic ether and stained for IgG, IgM, β_{1C}-globulin, C1q, and HBsAg.

Preparation and Serologic Studies of Eluates

The eluate was prepared from 500 serial frozen sections (5 μ thick, measuring approximately 5 × 5 mm) cut from the kidney cortex obtained from a patient with periarteritis nodosa (Table 1: M; 52 yr). All sections were mounted on slides, air-dried, and washed in four baths of PBS of 500 ml each for 1 hour to remove unbound HBsAg and protein. The slides were then placed in a beaker with 500 ml of 3 M NaSCN, pH 7.4, and eluted at room temperature by gently stirring for 3 hours. The NaSCN eluate was centrifuged at 900 × g for 20 minutes. The supernatant was dialyzed against PBS for 48 hours, and the globulin fraction of the clear eluate was precipitated with an equal volume of saturated ammonium sulfate solution. The precipitate was dissolved in PBS and then dialyzed against PBS for

Table 1—Histologic Data and Tissue Localization of HBV Antigens and HBsAg-anti-HBs Immune Complexes in Patients With Periarteritis Nodosa

Patients		Prevailing stage of vascular pathology	Histologic type of chronic glomerulonephritis	Histologic type of hepatitis	HBV antigens in liver		HBsAg-anti-HBs complexes		
Sex	Age (yr)				HBsAg	HBcAg	Blood vessels	Kidney glomeruli	Spleen and lymph nodes
M	27	I	Mesangial-proliferative	Chronic aggressive	+ +*	+ +	+	+	+
M	41	II	—	"Minimal"	+ + +	+ + +	+	-	NE
M	43	III	Membranoproliferative	Chronic persistent	+ +	+ +	+	+	+
M	44	III	Endocapillary and extracapillary proliferative	Chronic persistent	+	+	+	+	+
F	27	IV	Endocapillary and extracapillary proliferative	Chronic persistent	+ + +	+ +	+	+	+
M	52	IV	Mesangial-proliferative	Chronic persistent	+ +	+ + +	+	+	+
M	59	IV	Mesangial-proliferative	"Minimal"	+ +	+	+	+	NE

* Denote approximate amounts of HBV antigens.
NE = not examined.

72 hours. The portions of PBS used for initial elution and the NaSCN eluate were concentrated 250-fold by filtration in Amicon Ultrafiltration Cell, Model 52, equipped with UM 10 filter, and subsequently in Minicon B 15.

Control procedures consisted of a similar preparation of the eluate from kidney tissue obtained at necropsy of a patient with renal insufficiency who was seronegative for HBsAg but displayed rich granular and lumpy deposits of immunoglobulins in the kidney glomeruli.

The initial PBS eluates and the NaSCN eluates were examined for plasma proteins and individual immunoglobulins by immunodiffusion in agar (IDA) and immunoelectrophoresis (IEF). The presence of HBsAg was checked by IEOP and passive hemagglutination (PHA) (Hepanosticon–Organon); the presence of anti-HBs was checked by IEOP. Indirect immunofluorescence (IF) was used for the detection of anti-HBc.[12]

To control the effect of NaSCN treatment on the tissue HBsAg, serial sections from a liver that contained large amounts of HBsAg in the cytoplasm of hepatocytes were stained with FITC-labeled anti-HBs reagent after being washed in PBS for 1 hour and subsequently in NaSCN for 3 hours or in PBS for 4 hours.

Results

In 5 of the 7 patients, HBs–antigenemia persisted for 2 to 12 months. Persistently elevated transaminase (SGOT and SGPT) levels and abnormal liver functions tests were found in 4 patients. One patient had a history of a febrile icteric episode diagnosed clinically as acute hepatitis. Six patients developed hypertension. Six patients had a history of pulmonary tuberculosis treated with antituberculous drugs.

Histologic Studies

In all 7 cases, histologic examination of the tissue material revealed vascular lesions typical of "classic" periarteritis nodosa. These were recent insudative lesions with sparse perivascular inflammatory infiltrations consisting mainly of mononuclear cells, focal fibrinoid lesions (Figure 1), and older lesions with either focal or diffuse fibrous replacement of the media and obliteration of the lumen (Figure 2). The acute lesions were found mostly in smaller arteries; older lesions predominated in larger and medium-sized arteries. The classification of vascular lesions was based on histologic criteria described by Arkin [13] and modified by Zeek.[14] Morphologic features of vascular pathology typical of Stage IV of periarteritis nodosa prevailed in 3 cases; features of Stage III predominated in 2 cases; and features of Stage II or I were predominant in 2 cases. The histologic features of chronic glomerulonephritis coexisted in 6 patients. Five of these patients had chronic proliferative glomerulonephritis and 1 had chronic membranoproliferative glomerulonephritis. The morphologic changes in the liver were consistent with chronic persistent hepatitis in 4 cases, chronic aggressive hepatitis in 1, and "minimal" hepatitis [15] in 2 (Table 1). Dark brown globules of HBsAg were detected by the Shikata method in the cytoplasm of hepatocytes in all cases.

Immunofluorescent Studies

On immunohistochemical examination, variable amounts of HBsAg and HBcAg were disclosed in the cytoplasm and nuclei of hepatocytes in all cases. Granular and lumpy deposits of HBsAg were identified in vascular lesions of large, medium, and small arteries, arterioles, and kidney glomeruli. In small arteries, homogenous HBsAg deposits were localized diffusely throughout the intima which significantly narrowed or nearly occluded the lumen (Figures 3 and 4), chiefly at the points of branching (Figure 5). In larger arteries, HBsAg deposits were distributed along the elastic membrane, subendothelially and in the hyperplastic intima (Figure 6). On rare occasions, minute granular deposits of HBsAg were encountered on the endothelial surface and in the lumen of unchanged arteries. The most abundant deposits of HBsAg were identified in recent insudative and fibrinoid lesions and more frequently in smaller than in larger arteries. Older healed and healing lesions contained distinctly lesser amounts of HBsAg. As a rule, HBsAg deposits in blood vessel walls and kidney glomeruli (Figure 7) were accompanied by deposits of IgG (Figures 8 and 9), IgM (Figure 10), β_{1C}-globulin (Figure 11A), C1q (Figure 11B), and fibrin. The deposits of immunoglobulins appeared to be much more abundant than those of HBsAg and complement; however, their distribution pattern was similar. In 5 cases, granular deposits and lumpy masses comprising HBsAg (Figure 12A), immunoglobulins (Figure 12B), and complement were localized in the germinal centers of spleen and lymph nodes.

Double-staining with FITC-labeled anti-HBs reagent and LRB-labeled reagents for identification of IgG, IgM, and β_{1C}-globulin showed that the vascular deposits of HBsAg were an integral part of the immunoglobulin and complement deposits (Figure 13). When examined by incident light and filters for narrow-band excitation, these orange–yellow mixtures were resolved into the green fluorescence of HBsAg and the red fluorescence of immunoglobulins or complement.

Small granular or homogeneous deposits of fibrin were encrusted into the lesions in arteries and kidney glomeruli and were encountered in the germinal centers of spleen and lymph nodes.

Heterologous Complement Fixation

The pattern of fixation of guinea pig complement paralleled roughly that of the localization of IgG, IgM, β_{1C}-globulin, C1q, and HBsAg in serial sections. The reaction was most intensive in areas which contained a homogenous mixture of HBsAg and immunoglobulins. There was no fluorescence in sections incubated in control heat-inactivated guinea pig

serum or in sections stained directly with fluorescent anti-guinea pig β_{1C}-globulin reagent.

Elution Procedures

After 1 hour of washing in PBS, most of the immunoglobulins and all the HBsAg were removed from the interstitial tissue and the blood vessel lumina. However, the lesion content of the mixture of HBsAg, immunoglobulins, and complement remained practically unchanged. Subsequent washing of sections for 3 hours with a solution known to dissociate immune complexes resulted in a complete removal of HBsAg, β_{1C}-globulin, and C1q from vascular lesions and kidney glomeruli and a significant decrease in the amount of immunoglobulins in these areas. The strongest potential for dissocation of these deposits was displayed by 3 M NaSCN, 2.5 M KSCN, and 0.2 M HCl–glycine in the order of decreasing activity.

Subsequent to the washing of liver sections in PBS for 1 hour followed by NaSCN for 3 hours, or in PBS only for 4 hours, the amount of HBsAg in the cytoplasm of hepatocytes remained practically unchanged.

The examination by PHA of NaSCN eluate and individual portions of PBS obtained after initial elution showed HBsAg only in the first three of the four portions of PBS used for initial elution and in the NaSCN eluate. IgG was demonstrable by IDA and IEF in the NaSCN eluate and in the initial PBS eluate and in the PBS eluate from the control kidney. When tested by IEOP, these immunoglobulins did not contain anti-HBs. Anti-HBc activity was found only in the initial PBS eluate.

Discussion

The frequency of an association between periarteritis nodosa and persistent HBs–antigenemia has been reported by several authors.[1-5,16-19] HBsAg and or anti-HBs have been detected in 36.4% [4] to 69% [1] of serums from patients with histologically proved periarteritis nodosa. In the 7 unselected cases of periarteritis nodosa studied, the histologic changes in the liver varied from "minimal" to chronic aggressive hepatitis. The occurrence of HBsAg and HBcAg in the cytoplasm and nuclei of hepatocytes, as detected by direct immunofluorescence, indicated an ongoing infection with HBV. By serologic procedures, HBsAg was found in the serums of all these patients who were examined for the presence of this antigen.

In acute hepatitis the presence of circulating HBsAg–anti-HBs immune complexes, the fall of HBsAg and complement levels followed by the rise of anti-HBs levels and the return of complement levels to normal on recovery was considered indicative of immune elimination of HBsAg.[20-22]

This is supported by the finding of a mixture of HBsAg, immunoglobulins, and complement in the reticuloendothelial system at sites typical for trapping immune complexes.[23] Previous work from this laboratory demonstrated deposits compatible in composition with HBsAg immune complexes in the germinal centers of the spleen and lymph nodes in 72.9% of necropsy cases of various forms of acute and chronic hepatitis positive for HBV antigens.[24] In the present study similar deposits were identified in the germinal centers of the spleen and lymph nodes in 5 of the tested cases. These findings strongly suggest that circulating HBsAg immune complexes were present in the blood of these patients in the course of the disease. This assumption is supported by identification of HBsAg immune complexes in the serums of patients with periarteritis nodosa by electron microscopy [1,4,18] and rate zonal density-gradient centrifugation.[4,16]

In all the cases studied, granular and lumpy deposits of HBsAg, IgG, IgM, β_{1C}-globulin, and C1q were found in arteries and arterioles. In 6 cases, deposits were also detected in kidney glomeruli. That these deposits could represent HBsAg immune complexes was supported by demonstrating their strong avidity for guinea pig complement by immunohistochemical techniques. Further evidence was obtained by the successful elution of all HBsAg and part of the immunoglobulin content from these deposits by treatment with buffers known to dissociate antigen-antibody bonds but not with PBS. The results of the initial PBS washing of frozen sections before elution with NaSCN argue against the possibility of a nonspecific binding of HBsAg from the circulation to the preexisting vascular lesions. Attempts at identification of anti-HBs activity in the NaSCN eluate were unsuccessful, although IgG was detectable by IDA and IEF. However, the failure to demonstrate specific antibodies in such an eluate may be related to recombination of anti-HBs with eluted HBsAg after the dialysis of the NaSCN eluate against PBS and/or incomplete elution or denaturation of the eluted antibody.[25]

The presence of large masses of deposits compatible in composition and characteristics with HBsAg-anti-HBs immune complexes, chiefly in recent insudative and fibrinoid lesions, their lesser amounts in lesions undergoing involution, and their absence from healed lesions suggest that these complexes play a primary role in the pathogenesis of acute vascular damage in periarteritis nodosa. The absence of HBsAg immune complexes from older lesions may be related to their degradation and elimination from vascular walls. A rapid disappearance of immune complexes from the blood vessel walls was observed in the chronic BSA-anti-BSA rabbit system after the cessation of the daily antigen injections.[26]

Kidney glomerular deposits exhibiting characteristics typical of HBsAg

immune complexes were present in renal tissue from 6 of 7 patients studied. Glomerulonephritis associated with these immune complexes has been described.[9,27-29] By analogy to chronic viral infections in animals the nature of the glomerular lesions associated with arteritis in these patients suggests that the lesions are caused by persistent high levels of circulating immune complexes. The pathogenic significance of the process of the deposition of circulating virus antigen–antibody complexes in vessel walls and kidney glomeruli has been extensively studied in several experimental or naturally occurring virus infections in animals. From the immunomorphologic studies of tissues from mink chronically infected with Aleutian disease virus,[30] horses infected with equine arteritis virus,[31] and mice chronically infected with lymphocytic chroniomeningitis virus [32] it appears that the spectrum of vascular lesions and the character of deposits of immune reactants in the vessel walls are similar to these found in humans who have periarteritis nodosa and who are infected with HBV. The continuous production of large amounts of HBsAg in a significant number of patients infected with HBV, its release from hepatocytes into the circulation, the maintained anti-HBs production, and HBsAg immune complexes formation conform to similar events in chronic viral infections.[24,33]

As revealed in the present study and in studies by others, the strikingly high incidence of HBV infection in patients with periarteritis nodosa strongly suggests etiologic significance. Similarly, the demonstration of HBsAg immune complexes in recent insudative and fibrinoid vascular lesions provides substantial evidence for a primary pathogenic role of these complexes. All the present cases were classified as "classic" periarteritis nodosa; nevertheless, it is not unlikely that HBsAg immune complexes may play a similar role in other types of necrotizing vasculitis [2] analogically to various forms of glomerulonephritis associated with the deposition of HBsAg immune complexes in glomeruli.[9]

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Figure 1—Small artery from skeletal muscle in acute periarteritis nodosa showing fibrinoid necrosis and periarterial infiltration destroying the wall and extending into the periadventitial tissue. (H&E × 255)

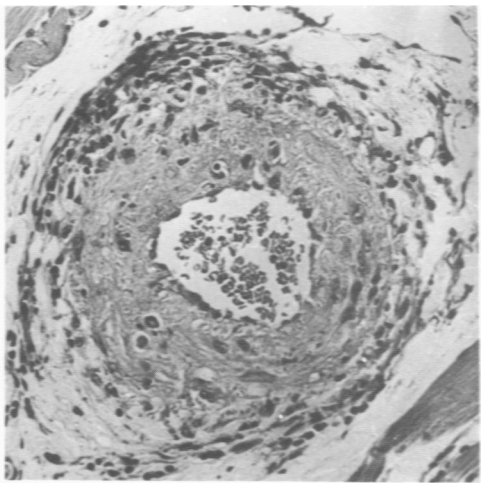
Figure 2—Kidney artery in healed periarteritis nodosa with complete obstruction of arterial lumen, destruction of elastica, and recanalization. (Elastic tissue stain, × 100)

Figure 3—Recent insudative lesion in a small artery from the pancreas with homogenous deposits of HBsAg in the thickened intima and media. (× 255)

Figure 4—Minute granular deposits of HBsAg in the greatly hyperplastic intima and in the lumen of a small artery in the kidney. Note segmental loss of internal elastic lamina. (× 255)

Figure 5—A branch of a small artery from the kidney with granular and lumpy deposits of HBsAg in the intima. (× 255)

Figure 6—A healed lesion of periarteritis nodosa in an artery from the kidney. Minute deposits of HBsAg along the internal elastic lamina in the fibrous tissue including arterial lumen. (× 255)



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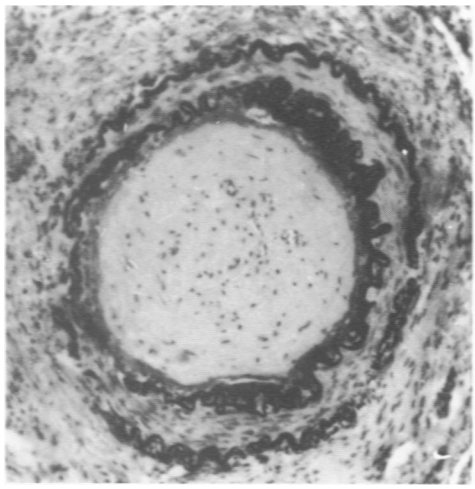

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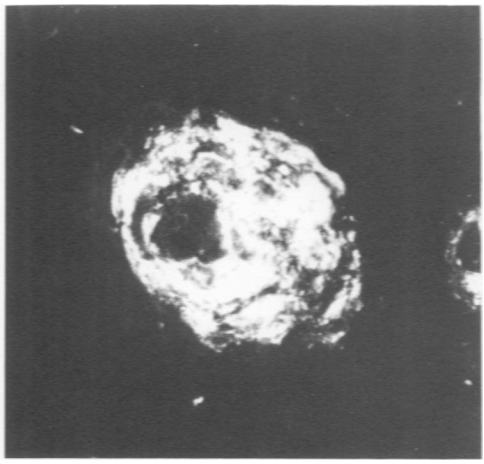

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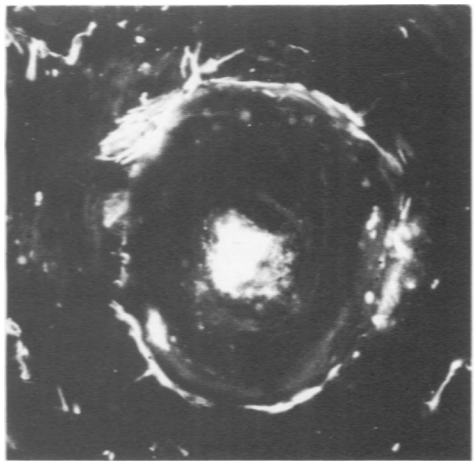

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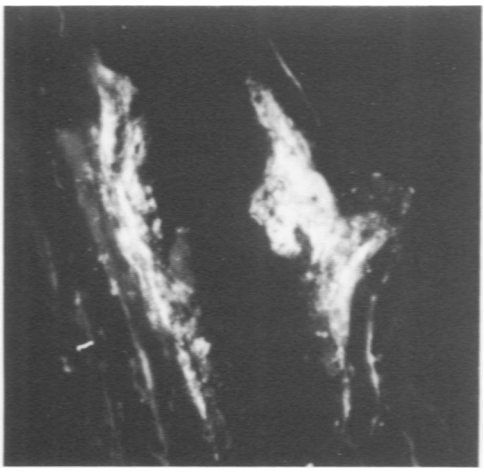

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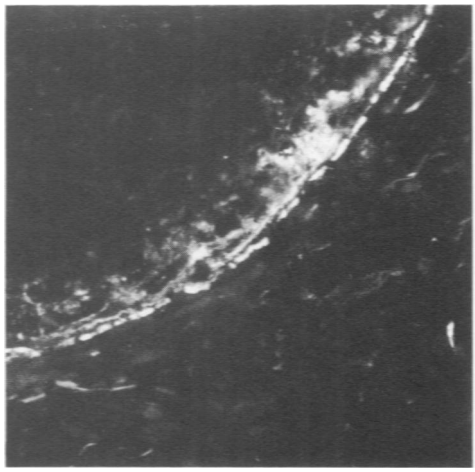

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Figure 7—Minute granular and lumpy deposits of HBsAg localized along the capillary basement membrane and mesangium of a glomerulus. (× 360)

Figure 8—A large lumpy deposit and delicate granular deposits of IgM localized along the capillary basement membrane of a glomerulus. (× 360)

Figure 9—Heavy deposits of IgG in the wall of three kidney arterioles. (× 255)

Figure 10—Irregularly dispersed deposits of IgM in the thickened intima and media of a small artery in the kidney. (× 255)

Figure 11—Fibrinoid necrosis of small arteries in the kidney with minute granular deposits of components of the complement. **A**—Localization of β_{1C}-globulin. **B**—Localization of C1q. (× 255)

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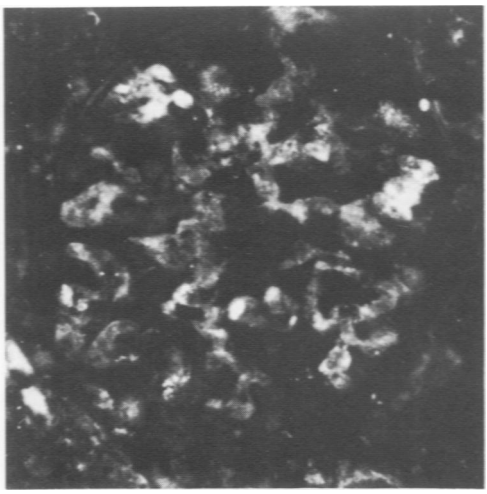

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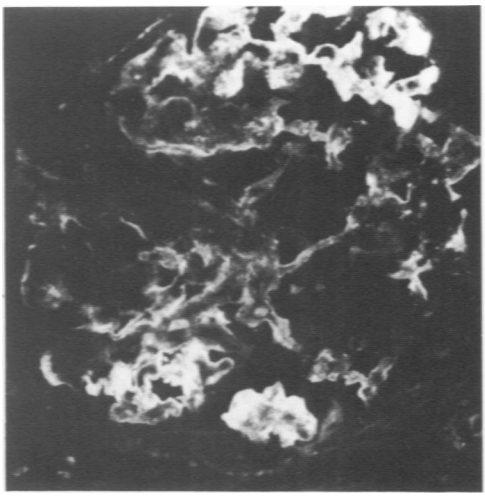

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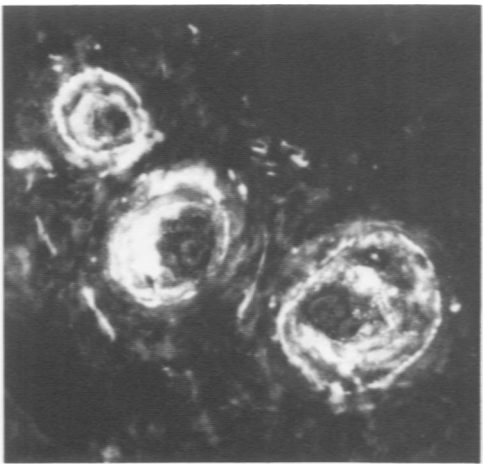

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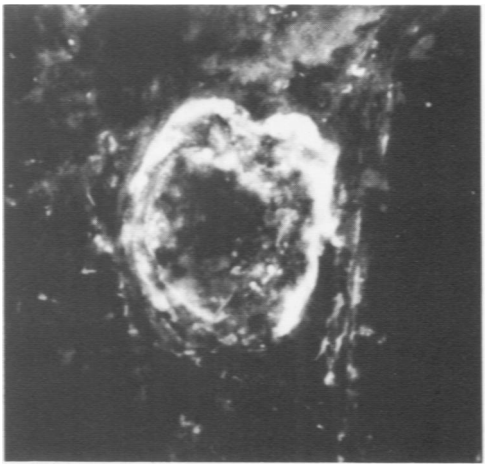

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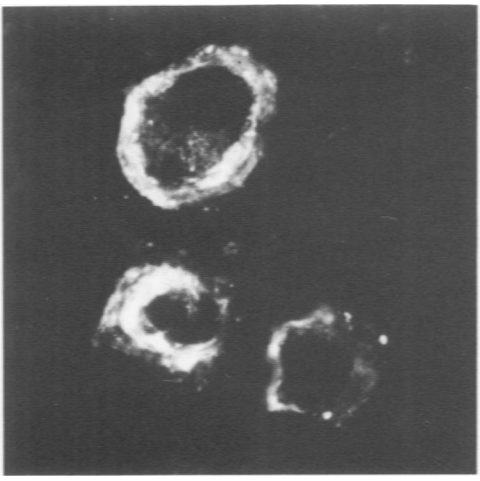
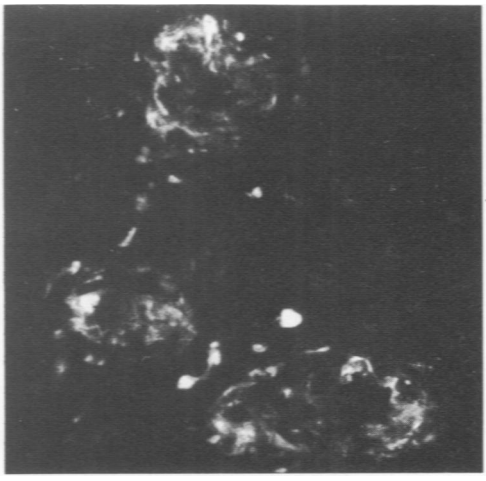
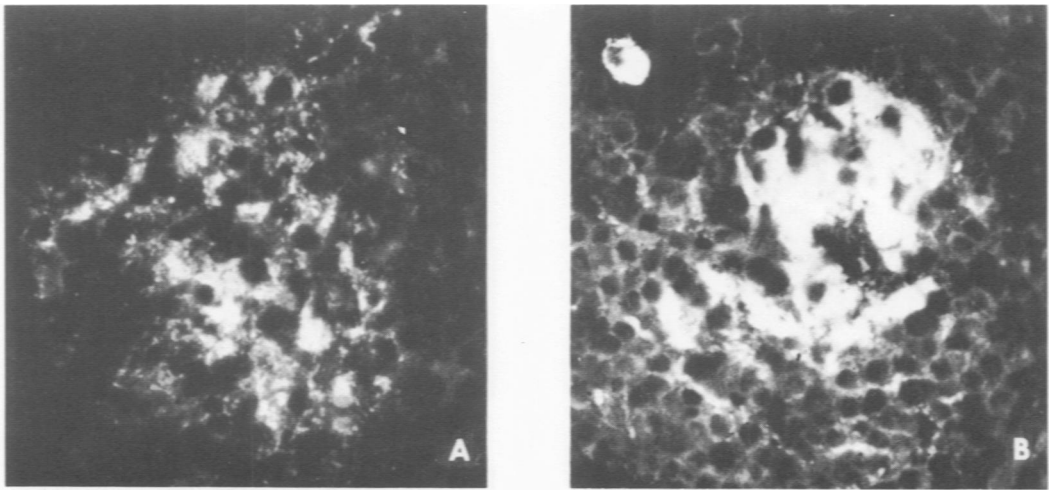


11B



12



13

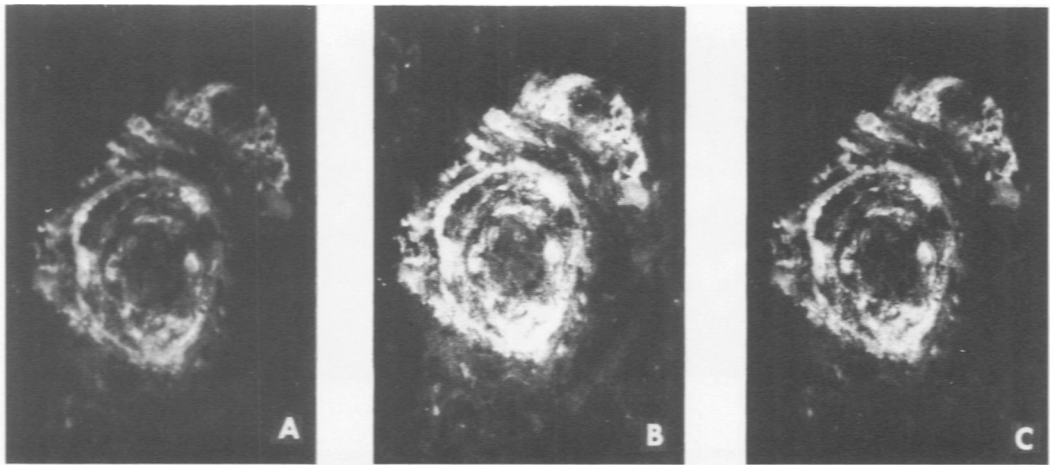


Figure 12—Serial consecutive sections of a lymph node showing an active germinal center. **A**—Localization of HBsAg deposits. **B**—Localization of IgG deposits. (× 360) **Figure 13**—Fibrinoid necrosis of a small artery from the kidney partially oblitered by and irregularly imbibed with the deposits of HBsAg and IgM. The fluorescent images were obtained by double-staining with FITC-labeled anti-HBs reagent and LRB-labeled anti-IgM reagent and by incident light and filters for narrow-band extitation of FITC and LRB. **A**—Pattern of HBsAg. **B**—Pattern of mixture of HBsAg and IgM. **C**—Pattern of IgM. (× 255)